Chapter 4

Impact of omission of surgery on survival of older patients with breast cancer

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Abstract

Background

Older patients with breast cancer are often not treated in accordance with guidelines. With the emergence of endocrine therapy, omission of surgery can be considered in some patients. The aim of this population-based study was to investigate time-trends in surgical treatment between 1995 and 2011, and to evaluate the effects of omitting surgery on overall and relative survival in older patients with resectable breast cancer.

Methods

Patients with stage I-III breast cancer aged 75 years and older diagnosed between 1995 and 2011 were selected from the Netherlands Cancer Registry. Time-trends of all treatment modalities were evaluated using linear regression models. Changes in overall survival were calculated with Cox regression. Relative survival was calculated with the Ederer II method.

Results

Overall, 26292 patients were included. The percentage of patients receiving surgical treatment decreased significantly, 90.8 per cent in 1995 to 69.9 per cent in 2011 ($P<0.001$). In the multivariable analysis overall survival did not change (hazard ratio 1.00 (95 per cent confidence interval (c.i.) 0.99 to 1.00 per year), nor did relative survival, relative excess risk 1.00 (0.98 to 1.02 per year).

Conclusion

Omission of surgery has increased in older patients with breast cancer during the last fifteen years in the Netherlands, but this did not alter overall or relative survival.

Introduction

Due to demographic changes an increasing proportion of breast cancer patients will be elderly.[1;2] The most recent guideline of the International Society of Geriatric Oncology (SIOG) states that all older patients with breast cancer with a resectable tumour should receive either a mastectomy or breast conserving surgery with whole-breast radiotherapy.[3;4] However, older patients are often not treated in accordance with these guidelines.[5;6]

A previous study showed that an increasing number of older patients with breast cancer in the Netherlands did not receive surgical treatment.[7] The most important reasons for omission of surgery were the patient's preference, high age, general health status, and comorbidity.[7] With the emergence of endocrine therapy, omission of surgery might be considered in some patients since the risk of surgical complications as well as the risk of dying from non-cancer-related causes increases with increasing age and number of comorbidities.[8-10]

Although several clinical trials have investigated tamoxifen as monotherapy compared to surgery in older patients with breast cancer,[11] extrapolation of the findings of clinical trials to the general breast cancer population, especially older patients, is difficult. Inclusion is often restricted based on comorbidity and functional status.[5] However, observational data may provide insight in the effect of omission of surgery in the older patient with breast cancer.

The aim of this study was to investigate time-trends in surgical treatment between 1995 and 2011 in a population-based cohort, and to evaluate the effects of different treatment strategies on overall and relative survival in older patients with resectable breast cancer.

Methods

Patients were selected from the Netherlands Cancer Registry. This registry identifies patients through the central pathology database. Trained personnel subsequently obtain patient, tumour and treatment characteristics from the patients' medical file. Follow-up status is available through linkage with municipal population registries.

All female patients with stage I-III breast cancer, aged 75 years and older and diagnosed between 1995 and 2011 were included in the study. Patients with a previous malignancy were excluded, with the exception of patients who had a history of basal cell carcinoma of the skin or a cervical intraepithelial neoplasia.

Estrogen-receptor (ER) and progesterone-receptor (PgR)-status were available from the year 2005 onwards. Stage was determined according to the pathological Tumour-Node-Metastasis (TNM)-stage according to the year of diagnosis. If histopathological tumour stage was missing, clinical tumour stage was used. Morphology was defined as ductal, lobular or other. The most extensive local and axillary surgery (sentinel node procedure or axillary lymph node dissection) were used for the analyses. Endocrine therapy, chemotherapy and radiotherapy were recoded as yes or no, since details about the specific therapies were lacking. Primary endocrine therapy was defined as endocrine therapy without surgery.

Statistical analyses

All analyses were performed in IBM SPSS Statistics version 20.0.. If data were missing, patients were analysed as a separate unknown group within the same variable. The main exposure of interest was surgical treatment, and the main outcomes were overall survival and relative survival.

Patients and treatment characteristics were assessed using chi-square tests. Time-trends of different treatment strategies were assessed using linear regression analyses with the percentage of patients receiving the specific treatment as the outcome, and the year of diagnosis as the independent variable.

Overall survival was calculated using Cox proportional hazard models. The year of diagnosis was assessed as the independent variable, with adjustments for patient characteristics. As cause of death is not available in the Netherlands Cancer Registry, relative survival over time was assessed by calculating the relative excess risk (RER) using the Ederer II method. This method calculates the ratio of the survival observed among the cancer patients divided by the survival of the corresponding general population, matched by age, sex, and year of diagnosis. National life tables were used to estimate the expected survival.

Assessing the effect of omitting surgery by directly comparing treated and untreated patients using straight forward Cox proportional hazard models would result in bias due to confounding by indication.[12] Therefore, the overall survival was calculated in Cox proportional hazard models using individual patient data with hospital as instrumental variable. This is a factor that determines treatment allocation but presumably unrelated to the outcome.[13] The cohort was divided into six groups based on the percentage of patients that was operated in the hospital of diagnosis (less than 70 per cent, 70 to 75 per cent, 75 to 80 per cent, 80 to 85 per cent, 85 to 90 per cent and more than 90 per cent). All analyses were adjusted for age, stage, ER status, PgR status and hospital of treatment in order to take possible differences in case-mix between hospitals into account. In addition, the analyses were adjusted for type of hospital

(university hospital, teaching hospital or other). Differences in relative survival between hospitals were assessed, using the Ederer II method as described above.

To compare differences in treatment strategies in different age-groups, additional sensitivity analyses were performed for patients aged 75-80 years and 80 years or older. All survival analyses were performed within the different stages (stage I, stage II, and stage III), and a sensitivity analysis was done using the percentage of operated patients as a continuous variable.

All statistical tests were two-sided, and a p value of less than 0.05 was considered as significant.

Results

Overall, 26292 breast cancer patients aged 75 years and older were included. The age-distribution changed over time, reflecting the ageing of the Dutch population; 3401 of 6953 (48.9 per cent) patients were aged 75-79 between 1995-1999, while only 1138 of 3473 (10.9 per cent) patients were aged 75-79 in 2010-2011 (P<0.001). Surgery was omitted in 4522 of 26292 (17.2 per cent) patients. Patients who did not receive surgical treatment were generally older, had more advanced tumour stage and more frequently had hormone-receptor positive disease (Table 1). Of 4522 patients not undergoing surgery, 3925 (86.8 per cent) patients received endocrine therapy. Only 509 (2.2 per cent) patients did not receive any form of oncologic treatment. In 11582 patients with known ER-status (e.g., diagnosed after 2005), radiotherapy was more frequently omitted in patients with ER-positive tumours, 7002 of 9828 (71.2 per cent) patients compared with 1001 of 1575 (63.6 per cent) patients with ER-negative tumours (P<0.001).

In general, most of the operated patients did not receive axillary surgery,19749 of 26292 (70.1 per cent) patients (Suppl. Table 1). Of 5427 (20.6 per cent) patients who received breast conserving surgery, some 4523 (75.2 per cent) patients underwent adjuvant radiotherapy. Most of the operated patients were also treated with adjuvant endocrine therapy, 15305 (52.3 per cent) patients, and 272 (1.0 per cent) patients received adjuvant chemotherapy.

A large variation in surgery rates was observed for all three hospital types; 69.3 to 92.6 per cent in university hospitals, 68.1 to 94.3 per cent in teaching hospitals, and 70.8 to 93.1 per cent in other hospital types.

Table 1 *Patient characteristics*

	All patients (n=26292)		**Surgically treated** (n=21770)		**Not surgically treated** (n=4522)		
	N	**%**	**N**	**%**	**N**	**%**	*P-value*
Period							
1995-1999	6953	(26.4)	6389	(29.3)	564	(12.5)	*<0.001*
2000-2004	7757	(29.5)	6705	(30.8)	1052	(23.3)	
2005-2009	8109	(30.8)	6234	(28.6)	1875	(41.5)	
2010-2011	3473	(13.2)	2442	(11.2)	1031	(22.8)	
Age-group							
75-79	10425	(39.7)	9876	(45.4)	549	(12.1)	*<0.001*
80-84	8890	(33.8)	7621	(35.0)	1269	(28.1)	
85-89	5056	(19.2)	3441	(15.8)	1615	(35.7)	
90+	1921	(7.3)	832	(3.8)	1089	(24.1)	
Tumour stage*							
I	7363	(28.0)	6339	(29.1)	1024	(22.6)	*<0.001*
II	14218	(54.1)	12072	(55.5)	2146	(47.5)	
III	4393	(16.7)	3308	(15.2)	1085	(24.0)	
Unknown	318	(1.2)	51	(0.2)	267	(5.9)	
ER-receptor							
Negative	1870	(7.1)	1687	(7.7)	183	(4.0)	*<0.001*
Positive	11633	(44.2)	8839	(40.6)	2794	(61.8)	
Unknown	12789	(48.6)	11244	(51.6)	1545	(34.2)	
PgR-receptor							
Negative	4370	(16.6)	3567	(16.4)	803	(17.8)	*<0.001*
Positive	8780	(33.4)	6735	(30.9)	2045	(45.2)	
Unknown	13142	(50.0)	11468	(52.7)	1674	(37.0)	
Type of hospital							
University hospital	1246	(4.7)	1022	(4.7)	224	(5.0)	*<0.001*
Teaching hospital	3065	(65.9)	14262	(65.5)	3065	(67.8)	
Other	1223	(29.3)	6479	(29.8)	1223	(27.0)	
Unknown	17	(0.1)	7	(0.0)	10	(0.2)	

*ER; Estrogen-receptor, PgR; progesterone-receptor *Stage was determined according to the pathological Tumour-Node-Metastasis (TNM)-stage according to the year of diagnosis*

Time-trends of treatment

Figure 1 shows time-trends for all treatments between 1995 and 2011. The percentage of patients receiving surgical treatment decreased significantly, 1186 of 1306 (90.8 per cent) patients were surgically treated in 1995 compared to 1214 of 1737 (69.9 per cent) patients in 2011(P<0.001). The decrease was similar in all three hospital-types (university hospital, teaching hospital and other hospital types (data not shown).

Primary endocrine therapy increased in the evaluated time-period, 93 of 1306 (7.1 per cent) patients received primary endocrine therapy in 1995 compared with 475 of 1737 (27.3 per cent) patients in 2011 (P<0.001). This increase was more pronounced among the oldest patients. The use of adjuvant endocrine therapy increased in patients aged 75-79 years, from 252 of 636 (39.6 per cent) patients in 1995 to 311 of 554 (56.1 per cent) patients in 2011 (P<0.001) and for patients aged 80-84 years 160 of 426 (37.6 per cent) patients in 1995 to 266 of 557 (47.8 per cent) patients in 2011 (P=0.022).

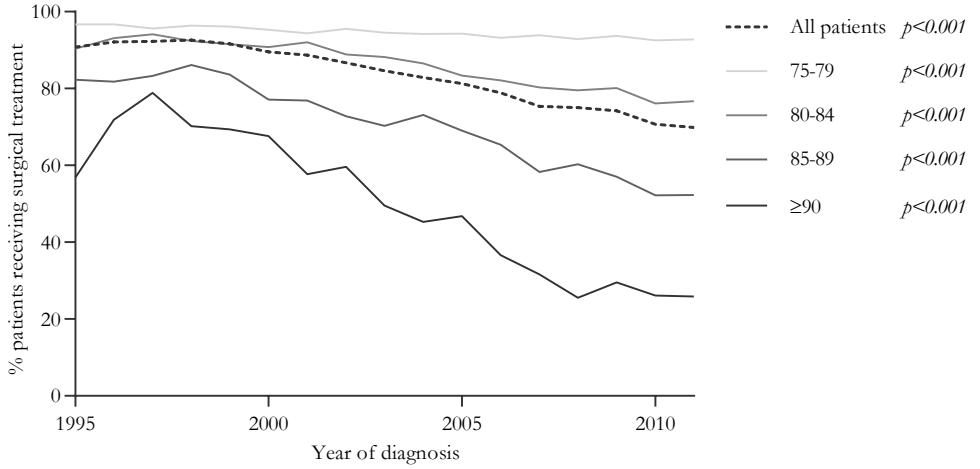
The percentage of patients receiving chemotherapy did not change over time for any age-group (data not shown). The use of radiotherapy after breast conserving surgery increased in all patients, 163 of 217 (75.1 per cent) patients received radiotherapy in 1995, while 347 of 406 (85.5 per cent) patients received radiotherapy in 2011 (P<0.001). Furthermore, the percentage of operated patients that received axillary surgery increased over time, nil of 217 patients in 1995 to 330 of 406 (81.3 per cent) patients in 2011 (P<0.001).

Survival analyses

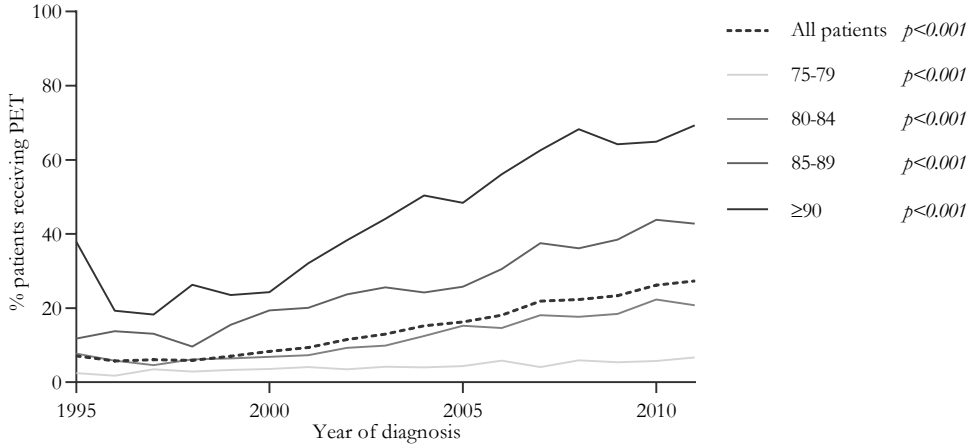
Follow-up was complete until December 31st 2011. Median follow-up for patients diagnosed between 1995 and 2011 was 3.7 years (range 0-16.9 years), and 4.0 years for patients who were still alive at the end of 2011 (0-16.9 years). In the multivariable analysis, overall survival did not change between 1995 and 2011 hazard ratio (HR) 1.00 (95 per cent confidence interval (c.i.) 0.99-1.00 per year, P=0.171 Figure 2). Overall survival improved slightly in patients aged 75-79 years, HR 0.99 (95% c.i. 0.98. to 1.00 per year, P=0.030), and decreased somewhat in patients

Figure 1 *Time-trends of different treatments per age-group*

1A *Surgical treatment of primary tumour*

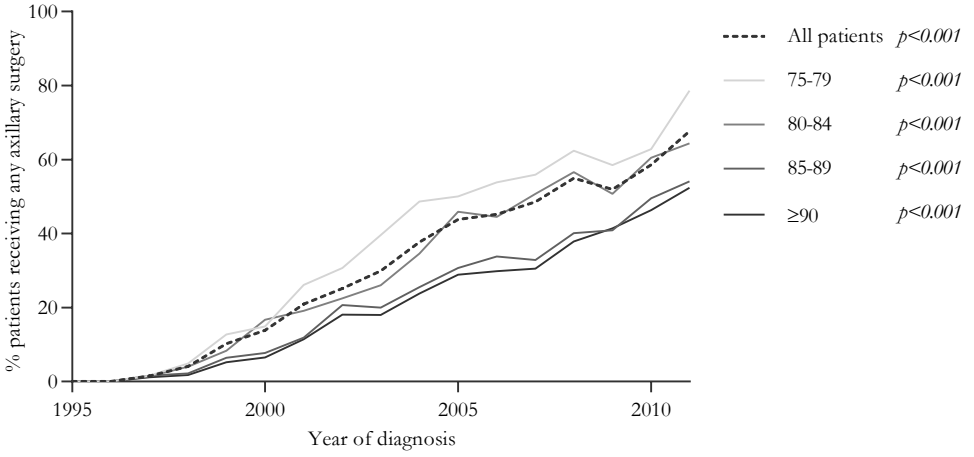


***1B** Primary endocrine therapy*



***1C** Radiotherapy after breast conserving surgery*

***1D** Any axillary surgery*



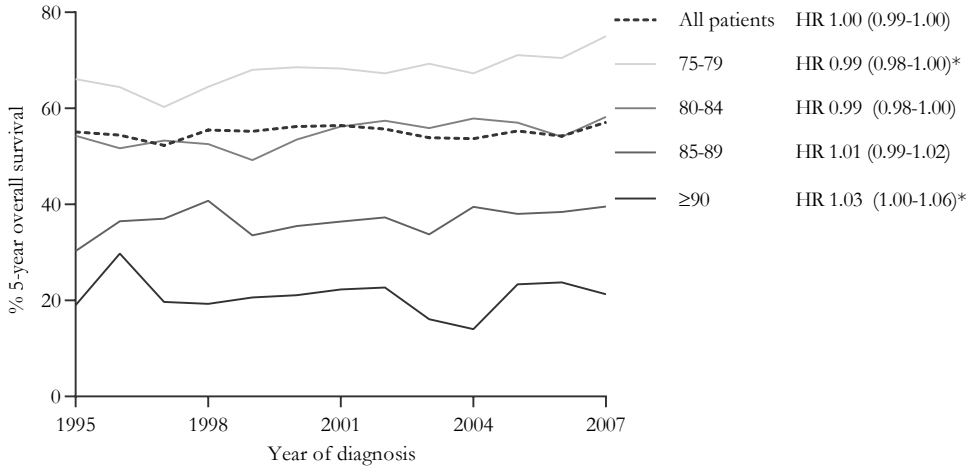
aged 90 years and older, HR 1.03 (95% c.i. 1.00 to 1.05 per year, P=0.026). In multivariable analysis, relative survival did not change during the included years (relative excess risk (RER) 1.00, 95% c.i. 0.98 to 1.02 per year, P=0.830). Similarly, stratified analyses showed no changes in relative survival for all age-groups (Figure 3).

The percentage of operated patients in the hospital of treatment did not influence the overall survival, (multivariable HR 0.86, 95% c.i. 0.66-1.12 for more than 90 per cent of patients operated in the hospital compared with hospitals that operated 70 per cent or less of the patients, P=0.088). Additional sensitivity analyses comparing overall survival rates between the hospital types within different age-groups showed similar results in both age-groups (data not shown). Relative mortality did not differ between hospitals in the multivariable analysis (RER 1.02, 95% c.i. 0.75 to 1.41 for hospitals that operated more than 90 per cent of patients, compared to hospitals that operated less than 70 per cent of the patients, P=0.347).

Discussion

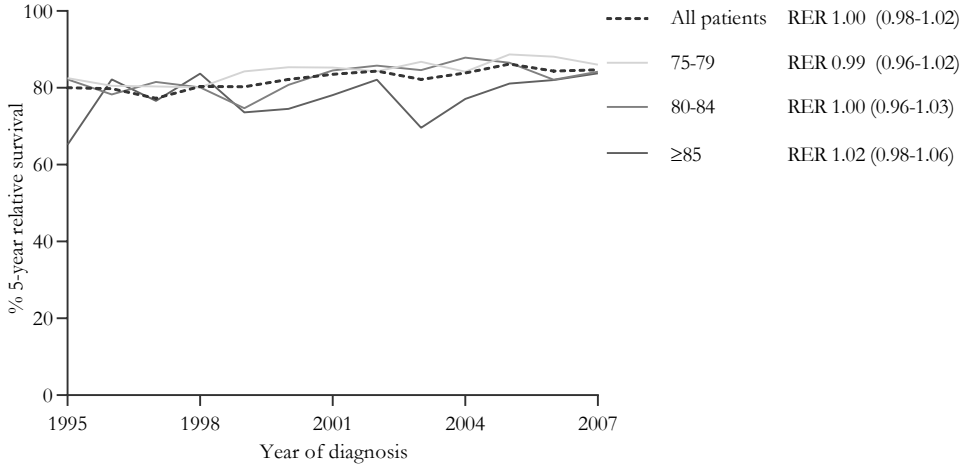
This study shows that the proportion of older patients with stage I-III breast cancer that did not receive surgical treatment has increased considerably over the past 15 years, as has the proportion of patients that received primary endocrine therapy. However, overall and relative survival did not change during the time period. No differences in overall and relative survival were observed between treatment strategies of different hospitals.

Figure 2 *Five year overall survival over the years per age group*



**p<0.05. HR=Hazard Ratio per year, adjusted for age, stage, and hormone receptor status. Median follow-up 5.5 years.*

Figure 3 *Five year relative survival over time per age-group*



RER=Relative Excess Risk per year, adjusted for age, stage, morphology and hormone receptor status. Median follow-up 5.5 years.

Currently, the Dutch guideline recommends performing either a mastectomy or breast conserving surgery followed by radiotherapy in all patients with resectable breast cancer.[14] This study shows that this guideline is not adhered to in an increasing number of patients. These findings may be explained by increased patient participation in clinical decision making, as a previous study showed that omission of surgery is most often due to patients' preference.[7] A previous meta-analysis which evaluated clinical trials that investigated tamoxifen as monotherapy compared with surgical treatment, showed no difference in overall survival despite a somewhat poorer loco-regional control[11] . This finding may have influenced daily clinical practice. Interestingly, overall and relative survival rates have not changed in the past 15 years, except in patients aged 75-79 for whom overall survival has marginally improved. The latter is likely due to an increased life-expectancy of the general population, as the relative survival of this group did not improve and the findings are thus of dubious clinical significance. Analyses that compared different treatment strategies between hospitals showed no differences in overall and relative survival. Hence, the findings of this study imply that the current therapies, including the omission of surgery, the use of primary and adjuvant endocrine therapy and the increase of axillary surgery, has not influenced the overall and relative survival in this patient group.

Several factors may have contributed to negating the effects of omitting surgical treatment. The most important factor is most likely the increased use of adjuvant endocrine therapy, despite the fact that this was only received by 40 to 60 per cent of patients. Further, the use

of axillary surgery has increased over time, most likely due to the gradual adoption of the sentinel node procedure. The additional information on tumour stage that this provides may have contributed to improved decision making concerning adjuvant therapy. An increasing number of patients that received primary endocrine treatment are probably more likely to be treated with aromatase inhibitors instead of tamoxifen, although this was not evaluated in the present study. Aromatase inhibitors have been demonstrated to be superior to tamoxifen in a neoadjuvant setting,[15;16] and could potentially be superior as monotherapy, although the ESTEeM trial, which set out to compare surgery with aromatase inhibitors as primary treatment for patients aged 75 years and older, was closed prematurely due to poor patient recruitment.[17;18]

Another likely explanation for the absence of differences of survival rates between different treatment strategies may be that the likelihood of dying from causes other than breast cancer increases with age and comorbidity.[8;19] Nonetheless, the median life-expectancy for an 85-year-old woman in the Netherlands is 6.6 years,[20] leaving sufficient time to suffer the consequences of inadequately treated breast cancer.

As overall survival has improved for younger patients with breast cancer in recent years,[21] one might thus argue that older breast cancer patients are generally undertreated compared to their younger counterparts: in many of the older patients did undergo surgery, and axillary staging and adjuvant endocrine treatment were omitted. This is a worrying alternative conclusion based on the results in the present investigation. In agreement, a large proportion of the oldest patients who were treated with breast conserving surgery did not receive subsequent radiotherapy, possibly out of fear for toxicity.

Functional outcomes should be taken into consideration when making treatment decisions for older patients[22]. Omission of surgery may lead to poor loco-regional control,[11] which may result in poor quality of life and a decline of functional status. Possibly, quality of life assessments may help to improve individualised clinical decision making in older patients[23].
Ideally, guidelines for treatment of older patients should be based on results from clinical trials. However, clinical trials generally include only fit older patients,[5] and as a result, extrapolation of findings from clinical trials to the general older population is not possible. This observational study assessed the effects of surgery on overall and relative survival by evaluating treatment strategies and the effects on survival over time, and subsequently by using the different hospitals as instrumental variable. This methodological approach is a major strength of this paper. Another strength of the study is the use of data from the Netherlands Cancer Registry, as it provides well-registered, reliable data in large numbers of patients.

This study has some important limitations. First, the proportion of patients who received surgery did not strongly differ between the different hospitals. However, this study involves a very large number of patients, meaning that even small differences in survival would have appeared in the results. By evaluating overall and relative survival over time, it was possible to investigate the effects of omitting surgery on overall and relative survival. A more important weakness is that it could be argued that hospital was not the most reliable instrumental variable, as it might be related to the outcome of patients. It was not possible to assess breast cancer specific survival, as causes of death were not available. However, it is well-known from previous studies that relative survival can be used as a valid proxy for cancer specific survival.[24] This method is particularly useful in the older population as determining cause of death in older patients can be notoriously difficult, as unexpected or unexplained deaths as may incorrectly be attributed to the cancer.[25;26] An important consideration is that increased omission of surgery was not the only change in treatment strategy over time, which makes it impossible to attribute survival trends to the omission of surgery only. Data on specific tumour biology were not available for patients who were diagnosed before 2005, but it is unlikely that the tumour biology of the entire population has strongly changed over the years. Finally, detailed patient and treatment characteristics such as comorbidity status, functional status, secondary treatments disease recurrence, and loco-regional disease control were not available for analysis.

With the above limitations, this study showed that the omission of surgery and the use of primary endocrine therapy have increased in older patients with resectable breast cancer in the last fifteen years, while both relative and overall survival remained unchanged.

Suppl. Table 1 *Treatment characteristics*

	All patients (n=26292)	
	N	**%**
Most extensive surgery		
None	4522	(17.2)
Breast conserving surgery	5427	(20.6)
Mastectomy	16343	(62.2)
Most extensive axillary surgery		
None	19749	(75.1)
Sentinal node procedure	5941	(22.6)
Axillary lymph node dissection	602	(2.3)
Radiotherapy		
No	18301	(69.6)
Yes	7991	(30.4)
Radiotherapy after BCS		
No	1490	(24.8)
Yes	4523	(75.2)
Hormonal therapy		
No	10987	(41.8)
Yes	15305	(58.2)
Chemotherapy		
No	26020	(99.0)
Yes	272	(1.0)
Any treatment		
No treatment	509	(1.9)
Any treatment	25783	(98.1)

BCS; breast conserving surgery

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